How far is complex balancing from detailed balancing?

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Abstract

We clarify the relation between the algebraic conditions that must be satisfied by the reaction constants in general (mass–action) kinetics systems for the existence of detailed or complex balancing equilibria. These systems have a wide range of applications in chemistry and biology [5, 14, 26, 27, 16, 23]. Their main properties have been set by Horn, Jackson and Feinberg [8, 10, 11, 18, 19, 20, 21]. We expect to extend our point of view to the study of qualitative features of the dynamical behavior of chemical interactions in molecular systems biology.

Keywords: General Kinetics, Mass Action, Complex Balancing, Detailed Balancing.

1 Introduction

In this article we clarify the relation between the algebraic conditions that must be satisfied by the reaction constants in general mas–action kinetics systems for the existence of detailed or complex balanced equilibria. The main properties of these systems have been set by Horn, Jackson and Feinberg [8, 10, 11, 18, 19, 20, 21], These systems have remarkable dynamic properties and have a wide range of applications in chemistry and biology [4, 5, 14, 15, 23, 16, 17, 26, 27].

We show that a reversible Horn–Jackson general mas–action kinetics system satisfying Feinberg's circuit conditions is detailed balanced if and only if it is complex balanced. In other words, under formal balancing conditions for the cycles (of the underlying undirected graph) of the reaction graph, both notions coincide. We formulate this property in terms of the algebraic equations defining the corresponding varieties in rate constant space.

In order to illustrate some of the definitions and concepts along the paper, we will use a reaction network diagram which represents a nonsequential multisite phosphorylation system with two sites, under mas–action kinetics. This network models, for example, the MEK-MKP3-ERK2 system

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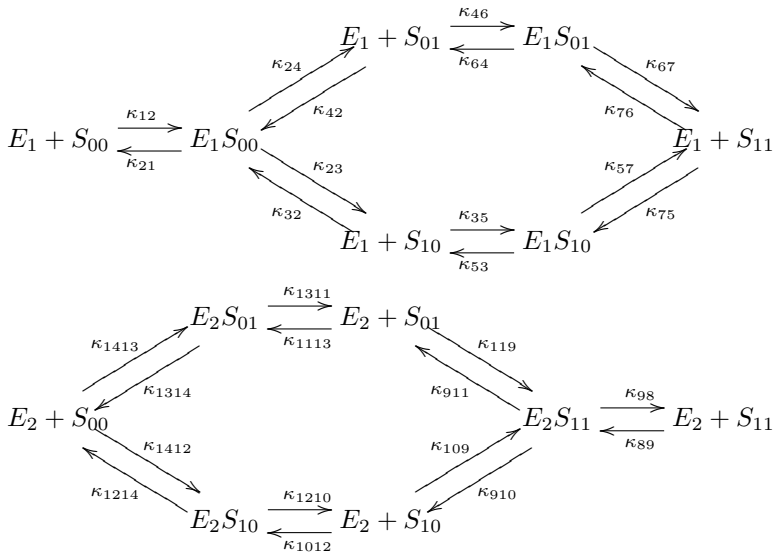
[23, 2, 12, 24]:



(1)

The four phosphoforms, S_{00}, S_{10}, S_{01}, S_{11}, are interconverted by the kinase E_1 and the phosphatase E_2. There are other six *species* $E_1S_{00}, E_1S_{10}, E_1S_{01}, E_2S_{11}, E_2S_{10}, E_2S_{01}$. [1]

Assuming mas–action kinetics, each reaction between two of the 14 *complexes* is annotated with the corresponding rate constant, indicated by a choice of numbering of the complexes. Although the rate constants κ_{32}, κ_{42}, κ_{75}, κ_{76}, κ_{109}, κ_{119}, κ_{1412}, κ_{1413}, are usually taken to be very small and so the corresponding reactions are omitted, we will not ignore them in this example because we are interested in special properties of the reaction constants in reversible networks.

In general, we will consider s species, with $c_1, c_2, \ldots, c_s$ representing their molar concentrations; a set of n complexes, and a numbered set E of e reactions between different complexes. The associated *chemical reaction network* is the finite directed graph $G = (V, E, Y)$, whose vertices V are labeled by the complexes $y_1, \ldots, y_n$ and whose edges E correspond to the reactions. We record the complexes by an $n \times s$-matrix of non-negative integers $Y = (y_{ij})$, which contains these stoichiometric coefficients. For instance, in the reaction diagram (1), we will name the 12 concentrations as $c_1, \ldots, c_{12}$ according to the following order of the species: S_{00}, S_{10}, S_{01}, S_{11}, E_1, E_2, E_1S_{00}, E_2S_{11}, E_1S_{10}, E_2S_{10}, E_1S_{01}, E_2S_{01}. The rows of the stoichiometric matrix $Y \in \{0,1\}^{14\times 12}$ are ordered according to the numbering of the complexes which is reflected in the names of the rate constants in diagram (1). For example, $y_1 = e_1 + e_5$, where e_i denotes the i-th canonical basis vector in $\mathbb{R}^{12}$, and the corresponding concentrations will be denoted by c_1, c_5.

We assume there is a non-negative continuous real-valued rate function $\mathcal{R}_{ij}(\mathbf{c})$ for each reaction (i, j) in the network, with the property that $\mathcal{R}_{ij}(\mathbf{c}) = 0$ if and only if $c_k = 0$ for some k in the support of y_i (that is, $y_{ik} \neq 0$). The reaction network (V, E, Y) endowed with a kinetics is called a *chemical reaction system* and we record this information in the notation as $G = (V, E, \mathcal{R}, Y)$. In a mas–action kinetics chemical reaction system, we simply have $\mathcal{R}_{ij}(\mathbf{c}) = \kappa_{ij}\mathbf{c}^{y_i}$, where $\kappa_{ij} \in \mathbb{R}_{>0}$ are the rate constants, and in this case the notations $G = (V, E, \kappa, Y)$ and $G = (V, E, \mathcal{R}, Y)$ will refer to the same system.

[1] In the MEK-MKP3-ERK2 system, E_1 would stand for MEK, E_2 for MKP3, S_{00} for ERK2, S_{11} for the doubly phosphorylated ERK2 (ppERK2) and S_{10} and S_{01} for the two monophosphorylated forms of ERK2 (the form phosphorylated on tyrosine, p$_Y$ERK2, or threonine, p$_T$ERK2, alone); also $E_1S_{00}, E_1S_{10}, E_1S_{01}, E_2S_{11}, E_2S_{10}, E_2S_{01}$ represent MEK·ERK2, MEK·p$_Y$ERK2, MEK·p$_T$ERK2, MKP3·ppERK2, MKP3·p$_Y$ERK2, MKP3·p$_T$ERK2, respectively.

The instantaneous rate of change of the concentrations c_k is given by:

$$\frac{dc_k}{dt} = \sum_{(i,j)\in E} (y_{jk} - y_{ik})\, \mathcal{R}_{ij}(\mathbf{c}), \quad k = 1, \ldots, s. \tag{2}$$

In what follows, we will assume *general mas–action kinetics*. In this case, the differential equations (2) can be written in the following form. Let A_κ denote the negative of the *Laplacian* of G. Hence A_κ is the $n \times n$-matrix whose off-diagonal entries are the κ_{ij} and whose row sums are zero. We denote by $\Psi(\mathbf{c})$ the vector $\Psi(\mathbf{c}) = (\mathbf{c}^{y_1}, \mathbf{c}^{y_2}, \ldots, \mathbf{c}^{y_n})$. For instance, in our example (1), $\Psi(\mathbf{c}) = (c_5c_1, c_7, c_5c_2, c_5c_3, c_9, c_{11}, c_5c_4, c_6c_4, c_8, c_6c_2, c_6c_3, c_{10}, c_{12}, c_6c_1)$. Then, the dynamical mas–action kinetics system (2) equals:

$$\frac{d\mathbf{c}}{dt} = \left(\frac{dc_1}{dt}, \ldots, \frac{dc_s}{dt}\right) = \Psi(\mathbf{c}) A_\kappa Y, \tag{3}$$

where $\mathbf{c}$ denotes the vector of species concentrations $(c_1(t), \ldots, c_s(t))$.

Definition 1.1. A *complex balanced* mas–action kinetics system is a dynamical system (3) for which the algebraic equations $\Psi(\mathbf{c})A_\kappa = 0$ admit a strictly positive solution $\mathbf{c}_0 \in \mathbb{R}^s_{>0}$. Such a solution $\mathbf{c}_0$ is a steady state of the system, i.e., the s coordinates of $\Psi(\mathbf{c}_0)A_\kappa Y$ vanish.

Remark 1.1. Clearly, a mas–action kinetics system (3) being complex balanced depends on both the digraph G and the rate constants κ_{ij}. A main property of complex balanced systems is that *all* strictly positive steady states $\mathbf{c}$ satisfy $\Psi(\mathbf{c})A_\kappa = 0$. They are *quasi-thermostatic* [21], which in the terminology of [3] means that the positive steady state variety is *toric*.

We will assume throughout the paper that digraphs $G = (V, E, Y)$ representing a chemical reaction network are *reversible*, i.e. if $(i, j) \in E$, then $(j, i) \in E$. We can thus identify G with the underlying undirected graph $\widetilde{G} = (V, \widetilde{E}, Y)$, where $\widetilde{E} = \{\{i, j\} : (i, j) \in E\}$.

Definition 1.2. A detailed balanced mas–action kinetics system is a dynamical system (3) for which the following algebraic equations admit a strictly positive solution $\mathbf{c}_0 \in \mathbb{R}^s_{>0}$:

$$-\kappa_{ij}\mathbf{c}_0^{y_i} + \kappa_{ji}\mathbf{c}_0^{y_j} = 0, \quad \text{for all} \quad \{i, j\} \in \widetilde{E}. \tag{4}$$

As it is for complex balanced mas–action kinetics systems, the condition of being detailed balanced depends on the graph $\widetilde{G}$ and the constants κ_{ij}.

Note that A_κ decomposes as the sum of $n \times n$ matrices $A_\kappa^{\{ij\}}$ for each undirected edge $\{i, j\} \in \widetilde{E}$ of the graph G, where in rows i, j and columns i, j the matrix $A_\kappa^{\{i,j\}}$ equals

$$\begin{pmatrix} -\kappa_{ij} & \kappa_{ij} \\ \kappa_{ji} & -\kappa_{ji} \end{pmatrix},$$

and all other entries of the matrix $A_\kappa^{\{i,j\}}$ are 0. Since the algebraic equation $-\kappa_{ij}\mathbf{c}_0^{y_i} + \kappa_{ji}\mathbf{c}_0^{y_j} = 0$ means that $\Psi(\mathbf{c}_0)A_\kappa^{\{i,j\}} = 0$, we see that every detailed balanced mas–action kinetics system is also complex balanced. The converse is not true in general. Again, a main property of a detailed balanced mas–action kinetics system is that *all* of its positive steady states $\mathbf{c}$ satisfy $-\kappa_{ij}\mathbf{c}^{y_i} + \kappa_{ji}\mathbf{c}^{y_j} = 0$ for every $\{i, j\} \in \widetilde{E}$.

For instance, in our example (1), for *any* choice of first order rate constant κ_1 and ssecond order rate constant κ_2 for which the value of κ_1 equals the value of κ_2 regardless of the corresponding

units, the mass–action kinetics system with the following rate constants is complex balanced but not detailed balanced:

$$\begin{array}{l}\kappa_{12}=\kappa_{46}=\kappa_{89}=\kappa_{1012}=\kappa_2\\ \\ \kappa_{24}=\kappa_{53}=\kappa_{67}=\kappa_{910}=\kappa_{1214}=\kappa_{1311}=\kappa_1\\ \\ \kappa_{32}=\kappa_{42}=\kappa_{75}=\kappa_{76}=\kappa_{109}=\kappa_{119}=\kappa_{1412}=\kappa_{1413}=\frac{1}{4}\kappa_2\\ \\ \kappa_{35}=\kappa_{1113}=\frac{3}{4}\kappa_2,\ \kappa_{23}=\kappa_{57}=\kappa_{64}=\kappa_{911}=\kappa_{1314}=\frac{3}{4}\kappa_1,\ \kappa_{21}=\frac{23}{4}\kappa_1,\ \kappa_{98}=\frac{47}{4}\kappa_1,\ \kappa_{1210}=\frac{69}{22}\kappa_1.\end{array} \tag{5}$$

For any $\alpha\in\mathbb{R}_{>0}$, the real vector in $\mathbb{R}^{12}_{>0}$ of the values of the molar concentrations of the different species $\mathbf{c}_{0,\alpha}=\alpha\,(23,17,11,47,1,2,4,8,14,11,13,16)$ is a positive steady state of the system for which $\Psi(\mathbf{c}_{0,\alpha})A_\kappa=0$, and hence the system is complex balanced. On the other side, for this choice of rate constants the system is *not* detailed balanced since (4) does not hold, for instance, for both $i_1=1$, $j_1=2$ and $i_2=10$, $j_2=12$ simultaneously that is, for the pairs of reactions

$$E_1+S_{00}\underset{\frac{23}{4}\kappa_1}{\overset{\kappa_2}{\rightleftarrows}}E_1S_{00}\,,\qquad E_2S_{10}\underset{\kappa_2}{\overset{\frac{69}{22}\kappa_1}{\rightleftarrows}}E_2+S_{10}.$$

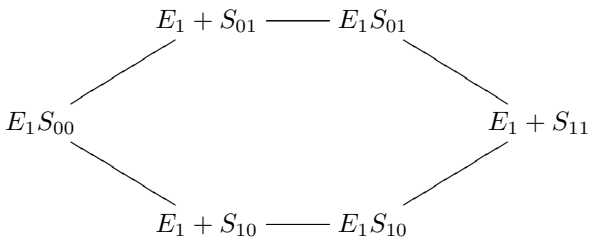
We now recall *Feinberg's circuit conditions* [10]. They correspond to linear relations which only depend on the structure of the reaction graph and not on the particular complexes. For every cycle $\widetilde{C}$ in $\widetilde{G}$, we will choose one direction and define C^+ as the cycle in G in that direction. C^- will be the cycle in the opposite direction. Although the directions are arbitrarily chosen, we will not worry about that since we will only need to distinguish between the two of them.

Definition 1.3. A formally balanced mas–action kinetics system is a dynamical system (3) for which the following circuit condition holds for every cycle $\widetilde{C}$ of $\widetilde{G}$:

$$\prod_{(i,j)\ in\ C^+}\kappa_{ij}=\prod_{(j,i)\ in\ C^-}\kappa_{ji}. \tag{6}$$

We will talk about formally balanced systems, although this definition can be applied to any digraph whose edges are reversible and labeled by constants κ_{ij}.

In our example (1), we can consider the cycle $\widetilde{C}$:



(7)

As (6) is not satisfied for $\widetilde{C}$, the system is not formally balanced.

Equations (6) show that the set

$$\mathcal{FB}_Y=\{\kappa=(\kappa_{ij})_{(i,j)\in E}: G=(V,E,\kappa,Y)\ is\ formally\ balanced\}$$

is an algebraic variety in $\mathbb{R}^e_{>0}$, i.e., it is cut out by polynomial equations in the rate constants.

We will review in §2.1 the known conditions for detailed balance, which are relations among the rate constants. Proposition 1 will recast the results in [10, 25], which imply that the set

$$\mathcal{DB}_Y = \{\kappa = (\kappa_{ij})_{(i,j)\in E} : G = (V, E, \kappa, Y) \textit{ is detailed balanced}\}$$

is also an algebraic variety in $\mathbb{R}^e_{>0}$.

In turn, it follows from [3, Section 2] that the set

$$\mathcal{CB}_Y = \{\kappa = (\kappa_{ij})_{(i,j)\in E} : G = (V, E, \kappa, Y) \textit{ is complex balanced}\}$$

is a third algebraic subvariety of $\mathbb{R}^e_{>0}$ (see Proposition 4), called the *moduli space of toric dynamical systems* in [3].

As we have already remarked, $\mathcal{DB}_Y \subseteq \mathcal{CB}_Y$. In fact, the main Theorem in [10] shows that $\mathcal{DB}_Y \subseteq \mathcal{FB}_Y$.

In this paper we prove the following result for a mas–action kinetics dynamical system associated to a reversible chemical reaction system $G = (V, E, \kappa, Y)$:

Theorem 1.1. *Under the assumption of formal balancing, a reversible mas–action kinetics system is detailed balanced if and only if it is complex balanced. That is,*

$$\mathcal{CB}_Y \cap \mathcal{FB}_Y = \mathcal{DB}_Y. \tag{8}$$

Our result generalizes two particular situations in which it is known that the notions of detailed and complex balancing coincide: the case in which $\widetilde{G}$ has no cycles, and the case of deficiency zero networks for which $\mathcal{DB}_Y = \mathcal{FB}_Y$ ([10], see also Proposition 3 below).

Our algebraic approach follows the lines of [3]. Our arguments easily imply that (8) holds at the level of ideals (which are radical). We refrain from giving a more algebraic formulation since it is straightforward and our main concern is to clarify these notions in the framework of general mas–action kinetics systems.

In Section 2 we recall known results, mainly from [10, 25, 3], that we state in a language adapted to our setting. In Section 3, we introduce new quotient variables which allow us to characterize formal and complex balancing in terms of the rate constants, and which we use to organize the proof of Theorem 1.1 in Section 4.

In Section 5, following a suggestion of Martin Feinberg, we translate Theorem 1.1 to the setting of general kinetic systems in Theorem 5.1, and we express in Proposition 6 another necessary and sufficient condition for a complex balanced system to be detailed balanced.

2 Preliminaries

In this section we only consider reversible mas–action kinetics systems. Given a chemical reaction network $G = (V, E, Y)$, we will denote by $\widetilde{G} = (V, \widetilde{E}, Y)$ the associated undirected graph. Since we assume that G is reversible, there is no loss of information in passing to $\widetilde{G}$.

Choose a numbering of the set of reactions, that is of the set of edges E of G and form the signed incidence matrix $C_G \in \{-1, 0, 1\}^{n\times e}$ whose column associated to the reaction (i, j) has a -1 on row i, a 1 on row j and all other entries equal to 0. We denote by

$$N \;=\; \ker_{\mathbb{Z}}(Y^t \cdot C_G) \;\subset \mathbb{Z}^e, \tag{9}$$

the kernel over $\mathbb{Z}$ of the product matrix $Y^t \cdot C_G$. Another name for the kernel of a matrix is the (right) nullspace of the matrix.

Clearly, the vector with a 1 on its (i,j)-th coordinate and on its (j,i)-th coordinate (and all other coordinates equal to zero) lies in N. We could instead choose one direction for each pair of reactions $(i,j),(j,i)$ in any way to get a directed subgraph G' of G, and consider the associated signed incidence matrix $C_{G'}$, with integer kernel

$$N' = \ker_{\mathbb{Z}}(Y^t \cdot C_{G'}) \subset \mathbb{Z}^{\frac{e}{2}}, \tag{10}$$

since we can clearly reconstruct N' from N and vice versa.

Remark 2.1. For interested readers, we survey the different notations occurring in the literature for the nullspace N' in (10). In [10], it is the subspace spanned by the vectors $(\alpha_{i\to j})_{i,j}$ with (i,j) reactions in G'. In [25], it is the subspace spanned by the columns of the matrix λ (there, $Y^t \cdot C_{G'}$ is called C). In [29], it is the subspace spanned by the vectors $(\varepsilon_w)_w$ with $w = \{i,j\} \in \widetilde{E}$. Finally, it is the subspace spanned by the columns of the matrix B in [6], where N stands instead for the matrix $Y^t \cdot C_{G'}$.

We introduce the following variables, which are usually known as *equilibrium constants*:

Definition 2.1. Let $G = (V, E, \kappa, Y)$ be a reversible chemical reaction system defining a dynamical system as in (3). For each $(i,j) \in E$ we define

$$q_{ij} \;=\; \frac{\kappa_{ij}}{\kappa_{ji}}. \tag{11}$$

Clearly, $q_{ij}q_{ji} = 1$ for all $(i,j) \in E$.

2.1 Detailed balanced systems

Detailed balanced systems have been broadly studied. In 1989, Feinberg ([10]) and Schuster and Schuster ([25]) described necessary and sufficient conditions for detailed balance to occur. The latter conceived these conditions as a *generalization of Wegscheider's condition*, which states that for cycles of monomolecular reactions the product of the equilibrium constants (q_{ij}, according to our notation) around these cycles must be equal to unity. Feinberg grouped these conditions more structurally into *circuit and spanning forest conditions* (see § 3.1).

In accordance to our notations, Theorem in [10, Section 3] and Theorem 1 in [25] can be restated as follows. As usual, for any $z = (z_1, \ldots, z_m) \in \mathbb{R}^m$ and $\lambda = (\lambda_1, \ldots, \lambda_m) \in \mathbb{Z}^m$, z^λ will denote the product $\prod_{i=1}^m z_i^{\lambda_i}$.

Proposition 1. *A chemical reaction system, $G = (V, E, \kappa, Y)$, is detailed balanced if and only if*

$$q^\lambda = 1 \quad \text{for all } \lambda \in N, \tag{12}$$

where q denotes the vector $q = (q_{ij})_{(i,j)\in E}$.

In fact, it is possible to derive a proof of this proposition using the following basic result [7]:

Proposition 2. *Let $\mathbf{k}$ be a field and $a_1, \ldots, a_m \in \mathbb{Z}^s$. Given a vector $z = (z_1, \ldots, z_m) \in (\mathbf{k} - \{0\})^m$, there exists $x = (x_1, \ldots, x_s) \in (\mathbf{k} - \{0\})^s$ such that $z_i = x^{a_i}$ for all $i = 1, \ldots, m$ if and only if $z^\lambda = 1$ for all $\lambda \in \mathbb{Z}^m$ such that $\sum_{i=1}^m \lambda_i a_i = 0$.*

When $\mathbf{k} = \mathbb{R}$ and $z \in \mathbb{R}^m_{>0}$, which will be our case, an easy proof of Proposition 2 can be given by taking logarithms.

Proof (of Proposition 1). A positive vector $\mathbf{c}_0$ satisfies a binomial equation $-\kappa_{ij}\mathbf{c}_0^{y_i} + \kappa_{ji}\mathbf{c}_0^{y_j} = 0$ if and only if $\mathbf{c}_0^{y_i - y_j} = q_{ij}$. The result follows from Proposition 2 for $m = e$ and $\{a_1, \ldots, a_m\} = \{y_i - y_j, (i,j) \in E\}$. □

One can translate Conditions (12) into a finite number of equalities associated to a system of generators of N, as described in [10], or in general, by matrix algebra tools as in [25, 29]. In [6], a new formalism of *thermodynamic-kinetic modeling* is introduced, where detailed balanced is imposed.

2.2 The minors of A_κ

Let G be a reversible digraph corresponding to a chemical reaction network and call G_t, $t = 1, \ldots, \ell$, the connected components of G, with corresponding sets of vertices V_t and edges E_t. Up to renumbering, we can assume $A_\kappa = A_\kappa(G)$ is block diagonal, with diagonal blocks the corresponding matrices $A_\kappa(G_t)$ for the components $G_1, \ldots, G_\ell$. Following [3], we introduce the following definition:

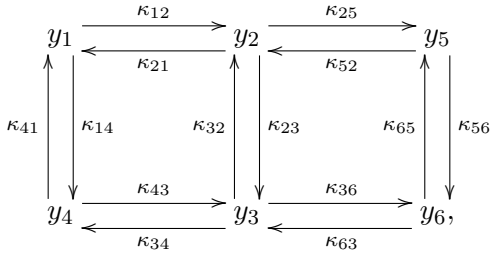
Definition 2.2. Consider any directed subgraph T of G such that the underlying undirected graph of T is a spanning forest of the underlying undirected graph of G. We denote the set of vertices of T by $V(T)$ and its set of edges by $E(T)$. Thus, $E(T)$ consists of $n - \ell$ edges. Fix a connected component G_t of G and write κ_t^T for the product of the $\#V_t - 1$ rate constants which correspond to all edge labels of the edges in $E(T) \cap E_t$. Let i be one of the nodes of G_t. The directed tree obtained by the restriction T_t of T to G_t is called an i-tree if the node i is its unique sink, i.e., all edges are directed towards node i. We will write κ^{T_t} for the product of the $\#V_t - 1$ rate constants which correspond to all edge labels of the edges of T_t. We introduce the following constants, which are polynomials in the (κ_{ij}):

$$K_i = \sum_{T_t \text{ an } i-tree} \kappa^{T_t}. \tag{13}$$

Note that each K_i is a nonempty sum of positive terms because, as G_t is strongly connected, there exists at least one i-tree for every vertex i and each $\kappa_{uv} > 0$ for $(u,v) \in E_t$.

It follows from the Matrix-Tree Theorem [28] that for any $i \in V_t$, the absolute value of the determinant of the submatrix of $A_\kappa(G_t)$ obtained by deleting the i-th row and any one of the columns, equals K_i. This (non-zero) minor is independent (up to sign) of the choice of columns because the row sums of $A_\kappa(G_t)$ are zero. Compare also with the statements in [22].

Example 2.1. We will introduce a new mathematical example only for the purpose of making the calculations more transparent. Let $G = (\{1,2,3,4,5,6\}, E, \kappa, Y)$ be the following connected chemical reaction system:



with $E = \{(1,2),(1,4),(2,3),(2,5),(3,4),(3,6),(5,6),(2,1),(4,1),(3,2),(5,2),(4,3),(6,3),(6,5)\}$.

For example, $K_1 = \sum_{T \text{ an } 1-tree} \kappa^T = \kappa_{21}\kappa_{32}\kappa_{63}\kappa_{41}\kappa_{52} + \kappa_{21}\kappa_{32}\kappa_{63}\kappa_{41}\kappa_{56} + \kappa_{21}\kappa_{32}\kappa_{63}\kappa_{43}\kappa_{52}$

$+\kappa_{21}\kappa_{32}\kappa_{63}\kappa_{43}\kappa_{56} + \kappa_{21}\kappa_{52}\kappa_{65}\kappa_{32}\kappa_{41} + \kappa_{21}\kappa_{52}\kappa_{65}\kappa_{32}\kappa_{43} + \kappa_{21}\kappa_{52}\kappa_{65}\kappa_{34}\kappa_{41} + \kappa_{21}\kappa_{52}\kappa_{65}\kappa_{36}\kappa_{41}$
$+\kappa_{21}\kappa_{52}\kappa_{65}\kappa_{36}\kappa_{43} + \kappa_{41}\kappa_{63}\kappa_{34}\kappa_{21}\kappa_{52} + \kappa_{41}\kappa_{63}\kappa_{34}\kappa_{21}\kappa_{56} + \kappa_{41}\kappa_{63}\kappa_{34}\kappa_{23}\kappa_{52} + \kappa_{41}\kappa_{63}\kappa_{34}\kappa_{23}\kappa_{56}$
$+\kappa_{41}\kappa_{63}\kappa_{34}\kappa_{25}\kappa_{56} + \kappa_{41}\kappa_{52}\kappa_{23}\kappa_{34}\kappa_{65}$.

2.3 The linear relations

We recall the structure of the nullspaces N and N' defined in (9) and (10). The statements that follow are all contained in [10] (with a different language).

The subsequent combinatorial arguments go back to Kirchoff. We can distinguish the following sublattice N'_1 of N'. It is the $\mathbb{Z}$-module spanned by the cycles of the underlying undirected graph $\widetilde{G}$. More precisely, given any oriented cycle $\mathcal{C}$ we form the vector $v_{\mathcal{C}} \in \{-1, 0, 1\}^{\frac{e}{2}}$ whose (i, j) coordinate equals 1 if the edge $(i, j) \in G'$ is in $\mathcal{C}$, -1 if instead the edge (j, i) lies in $\mathcal{C}$, and 0 if neither of the edges $(i, j), (j, i)$ is in $\mathcal{C}$.

The rank of N'_1 equals $\frac{e}{2} - n + \ell$, and a basis is formed by the *fundamental cycles* associated to a choice of a spanning forest T of G. The fundamental cycles associated to T are those (undirected) cycles which are created when we add an edge in the associated undirected graph $\widetilde{T}$ between any two vertices in the same connected component of G. Note that although the number of fundamental cycles in a graph is fixed, the cycles that become fundamental change with the spanning forest.

If we fix a spanning forest $\widetilde{T}$ of $\widetilde{G}$, we can moreover choose a direct complement N'_2 of N'_1 in N' as follows. Consider all vectors $v = (v_{ij},\, (i, j) \in E(G'))$ in N' such that $v_{ij} \neq 0 \Rightarrow \{i, j\} \in E(\widetilde{T})$. Call N'_2 the $\mathbb{Z}$-span of all these vectors v with support contained in $E(\widetilde{T})$. Then

$$N' \,=\, N'_1 \oplus N'_2.$$

The concept of deficiency δ of a chemical reaction network has been introduced and studied by Feinberg in a series of papers [9, 10]. With our notations, the deficiency of the network G equals $\delta = n - \dim S - \ell$, where S is the stoichiometric linear subspace defined by

$$S \,=\, \mathrm{span}\{y_i - y_j,\, (i, j) \in E\}.$$

Thus, $\dim S = \mathrm{rank}(Y^t \cdot C_{G'}) = \mathrm{rank}(Y^t \cdot C_G)$. As $\dim S = \frac{e}{2} - \mathrm{rank}(N')$, we get that $\mathrm{rank}(N'_2) = \delta$, so that $N'_2 = 0$ if and only if $\delta = 0$, and for $\delta > 0$ we could choose a system of δ generators of N'_2.

In a similar way, we can decompose N as $N = N_0 \oplus N_1 \oplus N_2$, where N_0 is the lattice of rank $\frac{e}{2}$ spanned by the $0, 1$ vectors in N which express the fact that the (i, j)-th column of $Y^t \cdot C_G$ is minus its (j, i)-th column, and N_i for $i = 1, 2$ is isomorphic to N'_i (we simply add 0 coordinates for the entries corresponding to the edges not in G').

3 Characterizing formally balanced and complex balanced systems

We keep the notations of § 2.

3.1 Formally balanced systems

We recall that our definition of formally balanced systems reformulates with our notation Feinberg's circuit conditions, which in the case of monomolecular reactions are also equivalent to Wegscheider's condition.

We can use the description of the kernel N in § 2.3 to translate our definition of formal balancing, similarly to the characterization of detailed balanced systems in Proposition 1.

Proposition 3. *Given a chemical reaction system, $G = (V, E, \kappa, Y)$, the following statements are equivalent:*

(i) The associated system is formally balanced,

(ii) For every cycle $\widetilde{C}$ of $\widetilde{G}$, it holds that

$$\prod_{(i,j)\ in\ C^+} q_{ij} \ = \ 1, \tag{14}$$

(iii) The vector $q = (q_{ij})_{(i,j)\in E}$ verifies

$$q^\lambda = 1 \quad \text{for all } \lambda \in N_1. \tag{15}$$

Then, a formally balanced system G is detailed balanced if and only if Equations (12) hold for all λ in a set of generators of N_2. These are the *spanning forest conditions* in [10].

3.2 Complex balanced systems

We now characterize mas–action kinetics complex balanced chemical reaction systems. We introduce new variables which are suitable for our formulations.

Definition 3.1. Let $G = (V, E, \kappa, Y)$ be a reversible chemical reaction system defining a dynamical system as in (3). For each $(i, j) \in E$, we define

$$Q_{ij} \ = \ \frac{K_j}{K_i}. \tag{16}$$

Remark 3.1. The following equations hold

$$Q_{ij}Q_{ji} \ = 1 \quad \text{for all } (i,j) \in E.$$

We define Q_{ij} by the same formula for any pair i, j in $1, \ldots, n$ and then

$$Q_{ij}Q_{jk} \ = Q_{ik} \quad \text{for all } i,j,k \in \{1,\ldots,n\}.$$

It turns out that the existence of a positive steady state $\mathbf{c}_0$ satisfying $\Psi(\mathbf{c}_0)A_\kappa = 0$ as in Definition 5.1, is again equivalent to algebraic conditions given purely in terms of the rate constants.

Proposition 4. *A chemical reaction system, $G = (V, E, \kappa, Y)$, is complex balanced if and only if*

$$Q^\lambda = 1 \quad \text{for all } \lambda \in N. \tag{17}$$

Here, Q denotes the vector $Q = (Q_{ij})_{(i,j)\in E}$.

The proof of Proposition 4 uses results from [3, Section 2]. We include it in the Appendix at the end of the paper, since it requires some background in commutative algebra.

Remark 3.2. From the definition of the vector Q, it is clear that the equalities $Q^\lambda = 1$ always hold for any $\lambda \in N_0 \cup N_1$. Therefore, it is enough to check Equalities (17) for λ in a basis of N_2. For instance, the rank of N_2 in (1) is 3. It is straightforward to check that for any choice of constants as in (5):

$$Q^1_{12} \times Q^1_{24} \times Q^1_{1113} \times Q^1_{1314} = \frac{K_1K_{11}}{K_4K_{14}} = 1$$

$$Q_{12}^1 \times Q_{23}^1 \times Q_{1012}^1 \times Q_{1214}^1 = \frac{K_1 K_{10}}{K_3 K_{14}} = 1$$
$$Q_{35}^1 \times Q_{57}^1 \times Q_{89}^1 \times Q_{910}^1 = \frac{K_3 K_8}{K_7 K_1 0} = 1,$$

which proves again that the system is complex balanced (without needing to show a complex balanced steady state).

4 Proof of Theorem 1.1

Consider a reversible mas–action kinetics chemical reaction system $G = (V, E, \kappa, Y)$ which is formally balanced. By Propositions 1, 3 and 4, we need to show that if the constants q_{ij} satisfy Equations (14), then

$$Q^\lambda = 1 \quad \text{for all } \lambda \in N$$

if and only if

$$q^\lambda = 1 \quad \text{for all } \lambda \in N.$$

These relations possibly involve constants associated to edges in several connected components of G. In fact, it holds that, modulo the formal balancing relations, an algebraic dependency relation $P(K) = 0$ among the (invertible) variables Q_{ij} holds for a polynomial P in e variables if and only if the "same" algebraic relation $P(q) = 0$ is true for the (invertible) variables q_{ij}. This is an immediate consequence of the following proposition.

Proposition 5. *Let $G = (V, E, \kappa, Y)$ be a reversible mas–action kinetics system which is formally balanced. Then,*

$$Q_{ij} \;=\; q_{ij} \quad \text{for all } (i,j) \in E. \tag{18}$$

Proof. Since Equations (14) relate variables q_{uv} for (u, v) in a single connected component of G, and since for given $(i, j) \in E$, i, j belong to the same component, we can assume G is connected.

Fix $(i, j) \in E$. We define a bijection between the set of j-trees and the set of i-trees as follows (see Example 4.1 for an illustration). Let T be any j-tree.

(i) If the edge $(i, j) \in E(T)$, then let T' be the tree obtained by replacing (i, j) by the opposite edge (j, i).

(ii) If the edge $(i, j) \notin E(T)$, let $\mathcal{C}_{ij}$ be the *undirected* fundamental cycle which is created in $\widetilde{T}$ by adding the edge (i, j). Call $\mathcal{C}_{ij}^+$ the corresponding *oriented* cycle which contains (i, j). Then, let T' be the tree obtained by giving to the edges of T which "lie" on $\mathcal{C}_{ij}$ the direction in $\mathcal{C}_{ij}^+$ (that is, we "reverse" all these edges in T).

It is straightforward to check that in both cases T' is, in fact, an i-tree and that the map $T \mapsto T'$ is a bijection. So, we have established a bijection between the terms in K_i and the terms in K_j.

Let T be a j-tree. We compare the term κ^T in K_j with the corresponding term $\kappa^{T'}$ in K_i. If $(i, j) \in E(T)$, we clearly have that

$$\kappa^T \;=\; q_{ij}\, \kappa^{T'}.$$

If instead we have that $(i, j) \notin T$ then

$$\kappa^T = \left(\prod_{(u,v) \in \mathcal{C}_{ij}^+, (u,v) \neq (i,j)} q_{vu} \right) \kappa^{T'}.$$

By the assumption of formal balance, we have that $\prod_{(u,v)\in\mathcal{C}_{ij}^+} q_{uv} = 1$ and so

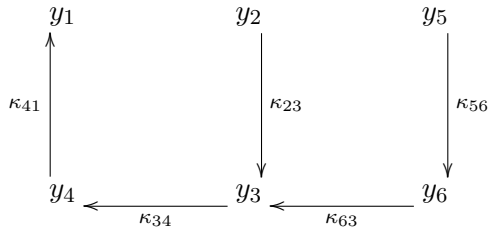
$$\prod_{(u,v)\in\mathcal{C}_{ij}^+,(u,v)\neq(i,j)} q_{vu} = q_{ij}.$$

Therefore,

$$Q_{ij} = \frac{K_j}{K_i} = q_{ij},$$

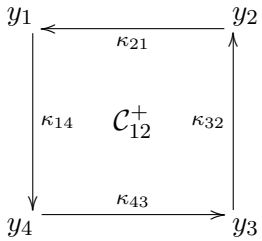
as wanted. □

Example 4.1 (Example 2.1 continued)**.** Choose the following 1-tree T:

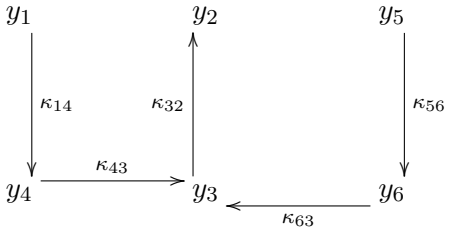


Let $(i,j) = (4,1)$. It is clear that by reversing the edge $(4,1) \in E(T)$ one gets a 4-tree.

Let now $(i,j) = (2,1)$, which does not lie in $E(T)$, and $\mathcal{C}_{12}^+$ be the corresponding oriented fundamental cycle:



Then, reversing the arrows in the cycle gives the following 2-tree T'



5 General kinetic systems

In this section we generalize Theorem 1.1 to non–necessarily mas–action kinetic systems in the sense of [9], see also [26, Section 2].

Let $G = (V, E, \mathcal{R}, Y)$ be a kinetic system as in the Introduction. The differential equations (2) that describe the corresponding dynamics can be written as

$$\frac{d\mathbf{c}}{dt} = \mathcal{R}C_G^t Y, \tag{19}$$

where $\mathcal{R}$ is the $1 \times e$ matrix with entries $\mathcal{R}_{ij}$, and C_G^t is the (transpose of) the corresponding signed incidence matrix we considered in Subsection 2.3.

Remark 5.1. It might be useful to compare our notation with the notation in [13, 1]. First, we consider a row velocity vector $\frac{d\mathbf{c}}{dt}$, while it is standard to consider the transposed column vector. So,

$$\left(\frac{d\mathbf{c}}{dt}\right)^t = \Gamma \mathcal{R}(\mathbf{c})^t, \quad \text{where } \Gamma = Y^t.C_G \in \mathbb{Z}^{s\times e}.$$

Assume we have a mas–action kinetics system. We denote by K the $n \times e$ real matrix with entry equal to κ_{ij} in row indicated by complex i and column indicated by the reaction edge (i, j), and equal to zero elsewhere. Then, $\mathcal{R}(\mathbf{c}) = \Psi(\mathbf{c})K$, the Laplacian matrix equals $A_\kappa = KC_G^t$ and we have

$$\frac{d\mathbf{c}}{dt} = \Psi(\mathbf{c})A_\kappa Y = \Psi(\mathbf{c})(KC_G^t)Y = \mathcal{R}(\mathbf{c})\Gamma^t.$$

In the notation of [13], Y^t is called Y_s, and the incidence matrices are denoted by $C_G = I_a, K^t = I_K$.

In this general context, we adapt the previous definitions.

Definition 5.1. A *complex balanced* kinetic system is a dynamical system (19) associated with the data $G = (V, E, \mathcal{R}, Y)$ for which the equations $\mathcal{R}C_G^t = 0$ admit a strictly positive solution $\mathbf{c}_0 \in \mathbb{R}^s_{>0}$. Such a solution $\mathbf{c}_0$ is a steady state of the system, i.e., the s coordinates of $\mathcal{R}C_G^t Y$ vanish. We call $\mathbf{c}_0$ a complex balancing equilibrium.

As before, we will assume that the digraph G is reversible, and thus identify G with the underlying undirected graph $\widetilde{G}$.

Definition 5.2. A *detailed balanced* kinetic system is a dynamical system (19) associated with the data $G = (V, E, \mathcal{R}, Y)$ for which the equations $\mathcal{R}_{ij}(\mathbf{c}) - \mathcal{R}_{ji}(\mathbf{c}) = 0$, for all $\{i, j\} \in \widetilde{E}$, admit a strictly positive steady state $\mathbf{c}_0 \in \mathbb{R}^s_{>0}$. We call $\mathbf{c}_0$ a detailed balancing equilibrium.

Again, every detailed balanced kinetic system is also complex balanced. To define formal balancing, we need to start from a particular positive steady state:

Definition 5.3. Given a complex balanced system at the positive steady state $\mathbf{c}_0 \in \mathbb{R}^s_{>0}$ corresponding to the data $G = (V, E, \mathcal{R}, Y)$, we say the kinetic system is *formally balanced at* $\mathbf{c}_0$ (or that $\mathbf{c}_0$ is a formally balancing equilibrium) if the following condition holds for every cycle $\widetilde{C}$ of $\widetilde{G}$:

$$\prod_{(i,j)\ in\ C^+} \mathcal{R}_{ij}(\mathbf{c}_0) = \prod_{(j,i)\ in\ C^-} \mathcal{R}_{ji}(\mathbf{c}_0). \tag{20}$$

We can now reformulate Theorem 1.1:

Theorem 5.1. *Consider a kinetic system* (19) *associated to the data* $G = (V, E, \mathcal{R}, Y)$ *with a complex balancing positive steady state* $\mathbf{c}_0 \in \mathbb{R}^s_{>0}$. *We have that* $\mathbf{c}_0$ *is a detailed balancing equilibrium if and only if it the system is formally balanced at* $\mathbf{c}_0$.

Proof. Given the complex balancing steady state $\mathbf{c}_0 \in \mathbb{R}^s_{>0}$, we define constants $\kappa_{ij} = \mathcal{R}_{ij}(\mathbf{c}_0)\mathbf{c}_0^{-y_i}$ for each $(i, j) \in E$ and we consider the mas–action kinetics dynamical system $\frac{d\mathbf{c}}{dt} = \Psi(\mathbf{c})A_\kappa Y$ associated with $G = (V, E, \kappa, Y)$. As $\mathcal{R}_{ij}(\mathbf{c}_0) = \kappa_{ij}\mathbf{c}_0^{y_i}$, we have $\Psi(\mathbf{c}_0)A_\kappa = 0$, and so this new mas–action kinetics system is complex balanced in the previous sense.

Moreover, as the kinetic system is formally balanced at $\mathbf{c}_0$, we have that

$$\prod_{(i,j)\ in\ C^+} \kappa_{ij} = C \prod_{(i,j)\ in\ C^+} \mathcal{R}_{ij}(\mathbf{c}_0) = C \prod_{(j,i)\ in\ C^-} \mathcal{R}_{ji}(\mathbf{c}_0) = \prod_{(j,i)\ in\ C^-} \kappa_{ji},$$

where $C = c_0^{-\sum_{i\in E(\widetilde{C})} y_i} \neq 0$. Then, the mas–action kinetics system associated with $G = (V, E, \kappa, Y)$ is formally balanced. By Theorem 1.1 it is detailed balanced. This means that every binomial $\kappa_{ij}\mathbf{c}^{y_i} - \kappa_{ji}\mathbf{c}^{y_j}$ vanishes at $\mathbf{c}_0$, implying $\mathcal{R}_{ij}(\mathbf{c}_0) - \mathcal{R}_{ji}(\mathbf{c}_0) = 0$, and so the kinetic system associated with $G = (V, E, \mathcal{R}, Y)$ is detailed balanced at $\mathbf{c}_0$. The other implication is clear. □

We end the paper by showing another necessary and sufficient condition for a complex balanced kinetic system to be detailed balanced.

Proposition 6 (Feinberg)**.** *Given a kinetic system* (19) *associated to the data* $G = (V, E, \mathcal{R}, Y)$ *with a complex balancing positive steady state* $\mathbf{c}_0 \in \mathbb{R}^s_{>0}$*, the following statements are equivalent:*

(i) The equilibrium $\mathbf{c}_0$ *is detailed balancing.*

(ii) For every cycle $\widetilde{C}$ *in* $\widetilde{G}$ *there exists an edge* $\{i_{\widetilde{C}}, j_{\widetilde{C}}\} \in E(\widetilde{C})$ *such that*

$$\mathcal{R}_{i_{\widetilde{C}} j_{\widetilde{C}}}(\mathbf{c}_0) - \mathcal{R}_{j_{\widetilde{C}} i_{\widetilde{C}}}(\mathbf{c}_0) = 0.$$

(iii) Property (ii) holds for every basic *cycle associated to any spanning forest of* $\widetilde{G}$*.*

Proof. The equivalence between (ii) and (iii) is clear, as well as the implication from (i) to (ii). To see that (iii) implies (i), let G' be the digraph obtained from G by "deleting" all edges $(i_{\widetilde{C}}, j_{\widetilde{C}}), (j_{\widetilde{C}}, i_{\widetilde{C}})$ in the corresponding directed cycle C, together with their labels, for all basic cycles $\widetilde{C}$. Then, the associated undirected graph $\widetilde{G'}$ has no cycles and so any positive complex balancing equilibrium $\mathbf{c}_0$ for G' is automatically also detailed balancing. Call $A_\kappa(\mathbf{c}_0)$ (respectively, $A'_\kappa(\mathbf{c}_0)$) the Laplace matrices of the mas–action kinetics system associated with G (resp. G') with reaction constants $\kappa_{ij} = \mathcal{R}_{ij}(\mathbf{c}_0)\mathbf{c}_0^{-y_i}$ for each $(i, j) \in E$ (resp. $\kappa_{ij} = \mathcal{R}_{ij}(\mathbf{c}_0)\mathbf{c}_0^{-y_i}$ for each $(i, j) \in E - \{(i_{\widetilde{C}}, j_{\widetilde{C}}), (j_{\widetilde{C}}, i_{\widetilde{C}}),\ \widetilde{C}$ a basic cycle of $\widetilde{G}\}$). But if $\mathbf{c}_0$ satisfies the conditions in (iii), it follows that

$$\Psi(\mathbf{c}_0)A'_\kappa(\mathbf{c}_0) \;=\; \Psi(\mathbf{c}_0)A_\kappa(\mathbf{c}_0) = 0.$$

Therefore, $\mathbf{c}_0$ is detailed balancing for G', which together with the equalities in (iii) implies that $\mathbf{c}_0$ is detailed balancing for G, as wanted. □

6 Conclusions

We studied the conditions in parameter space which ensure the existence of particularly well behaved dynamics in general (mas–action) kinetics chemical reaction systems and we compared from an algebraic perspective important classical notions. We plan to further apply this point of view to the study of biologically meaningful biochemical reaction networks, in particular those associated to enzymatic reactions as in [16, 23, 1, 5], where we expect that tools from elimination theory in the framework of algebraic varieties (and in particular, toric varieties), together with results in algebraic combinatorics (as the Matrix-Tree Theorem), will contribute to generalize current approaches.

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7 Appendix

We present here the proof of Proposition 4.

Proof. We first claim that a system $G = (V, E, \kappa, Y)$ defines a complex balanced system if and only if there exists a positive vector $\mathbf{c}_0 \in \mathbb{R}^s$ such that the following binomial equations are satisfied

$$K_i \mathbf{c}_0^{y_j} - K_j \mathbf{c}_0^{y_i} = 0, \text{ for all } (i,j) \in E. \tag{21}$$

To prove this claim, we form as in [3] the following binomial ideals in $\mathbb{Q}[\mathbf{c}] := \mathbb{Q}[c_1, \ldots, c_s]$:

$$I = I_1 + \cdots + I_\ell, \quad I_t = \langle K_i c^{y_j} - K_j c^{y_i}, (i,j) \in E_t \rangle, \, t = 1, \ldots, \ell. \tag{22}$$

Here $E_1, \ldots, E_\ell$ are the edges of the different connected components of G, as in Section 2. We moreover define the ideal T_G as the saturation

$$T_G = (I : (c_1 c_2 \ldots c_s)^\infty) = \{p \in \mathbb{Q}[\mathbf{c}] : \exists \, u \in \mathbb{Z}_{\geq 0} \text{ such that } p(c_1 c_2 \ldots c_s)^u \in I\}.$$

We denote by $V_{>0}(I)$ the positive variety of I, that is, the zeros of I in $(\mathbb{R}_{>0})^s$, and similarly for other ideals. As $T_G = (I : (c_1 c_2 \ldots c_s)^\infty) = (I_1 : (c_1 c_2 \ldots c_s)^\infty) + \cdots + (I_\ell : (c_1 c_2 \ldots c_s)^\infty)$, we deduce from display (8) in [3] that $V_{>0}(T_G) = \{\mathbf{c} \in \mathbb{R}^s_{>0} : \Psi(\mathbf{c}) A_\kappa = 0\}$. But a point x with all non-zero coordinates is annihilated by T_G if and only if it is annihilated by I. We then have that

$$V_{>0}(I) = \{\mathbf{c} \in \mathbb{R}^s_{>0} : \Psi(\mathbf{c}) A_\kappa = 0\},$$

and so the system G is complex balanced if and only if there exists a positive vector $\mathbf{c}_0$ satisfying Equations (21).

Now, we argue as in the proof of Proposition 1. These equations are equivalent to $c_0^{y_i - y_j} = Q_{ij}$ for all $(i,j) \in E$. By Proposition 2, for $m = e$ and $\{a_1, \ldots, a_m\} = \{y_i - y_j, (i,j) \in E\}$, these conditions are in turn equivalent to $Q^\lambda = 1$ for all $\lambda \in N$, as stated. $\square$